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Assessing the Clinical Utility of Liquid Biopsies Across 5 Potential Indications From Therapy Selection to Population Screening
A Review

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IMPORTANCE There has been great enthusiasm for the emerging technology of molecular-based tests to detect and quantify tumor DNA circulating in the bloodstream, colloquially known as a liquid biopsy. However, less attention has been given to how their clinical utility depends on the indication for testing, which includes a range of clinical situations, each presenting unique challenges.

OBSERVATIONS Five indications for circulating tumor DNA (ctDNA) blood testing were considered. (1) For therapy selection, ctDNA tests can identify genetic alterations in patients with cancer amenable to targeted therapy, but most patients do not have a targetable alteration. (2) For response to therapy, the absence of residual tumor DNA following cancer surgery could reduce the use of adjuvant chemotherapy, but it is unclear that this will happen in practice. (3) For disease surveillance following cancer treatment, ctDNA tests may well detect cancer recurrence before symptoms appear, yet earlier intervention may have no effect on mortality. (4) For diagnosis of suspected cancer, ctDNA tests are able to identify some symptomatic cancers, but how they add to the conventional diagnostic evaluation is unknown. (5) For screening for cancer, multicancer tests can detect many types of cancer, but their low sensitivity for early-stage tumors raises questions as to whether screening can help patients live longer or live better.

CONCLUSIONS AND RELEVANCE Circulating tumor DNA tests are being promoted for multiple indications. Numerous studies are ongoing, but randomized clinical trials of their effect on patient-centered outcomes are rare. While these tests have the potential to improve care in selected indications, this must be proven, as they will add cost, complexity, and unintended adverse effects for patients.

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The emerging category of tests that use body fluids to measure circulating levels of tumor cells, proteins, tumor markers, or circulating nucleic acids (DNA or RNA) has been colloquially known as a liquid biopsy.[1,2] Herein, we focus primarily on molecular-based tests to detect and quantify tumor DNA circulating in the bloodstream (circulating tumor or ctDNA).

Ideally, evaluations of a new diagnostic test would ascend the hierarchy of first demonstrating analytic validity, then clinical validity, and finally clinical utility.[3] Analytic validity addresses the question: Does the test reliably measure what it purports to measure? (ie, Is the test result positive when the genetic alteration is present?) Clinical validity addresses the question: Does the test result accurately identify the patient's clinical status? (ie, Does the genotype accurately reflect the phenotype?) Clinical utility addresses a larger question: Does testing meaningfully improve patient outcomes?

In practice, however, the evaluation process can be subverted. Proponents may instead simply appeal to biological plausibility and assert that there must be value to knowing about ctDNA. They may perform the least amount of evaluation needed to demonstrate some analytic and clinical validity. They may then vigorously promote the technology and hope it becomes enmeshed in clinical practice before any rigorous evaluation can be performed. Perhaps they even try to garner a bipartisan majority in Congress to sponsor legislation mandating Medicare payment for ctDNA screening tests—as has in fact happened.[4,5]

While there is considerable enthusiasm for comprehensive cancer genomic testing of ctDNA, there is much work to be done to demonstrate clinical utility. Herein, we consider the central clinical question for 5 possible indications. While ctDNA tests have the potential to improve care in selected clinical settings, there is also a risk of adding cost and complexity to the system, as well as unintended adverse effects for patients.

Therapy Selection

Background and Theoretical Case

The most established use of ctDNA testing is for therapy selection in patients known to have cancer. Targeted treatment—therapies directed toward specific genetic alterations in the tumor—have become increasingly available for a variety of cancers.[6] The tradi-

tional method to determine whether targetable alterations are present is to test the tumor itself. Circulating tumor DNA offers a useful alternative for patients who have limited tissue for molecular testing or who are not candidates for tumor resection (eg, because of inoperable disease).

Testing of ctDNA could provide a tumor's molecular signature earlier and allow for better targeted neoadjuvant therapy, rather than waiting for a biopsy or tumor resection for tissue-based testing. These tests may also provide a more comprehensive snapshot of the heterogeneity of the tumor and/or its metastatic lesions, as blood samples contain ctDNA from all components of the tumor as opposed to that obtained from a single tissue sample.[7,8] This could facilitate the detection of drug-resistant subclones and better inform therapy. However, to our knowledge, these theoretical advantages have not been documented to improve patient outcomes.

Evidence Base

In 2016, the US Food and Drug Administration approved the first ctDNA test to detect 2 alterations in the *EGFR* gene in patients with non–small cell lung cancer to determine their eligibility for the epidermal growth factor receptor inhibitor erlotinib hydrochloride.[9] Subsequently, other ctDNA tests using next-generation sequencing have been approved, allowing the testing of multiple alterations across many genes[10,11] (PGDx elio plasma resolve [Personal Genome Diagnostics] tests 33 genes[12]; Guardant360 CDx [Guardant Health], 55 genes[13]; and FoundationOne Liquid CDx [Foundation Medicine, Inc], 324 genes[14]).

Using tissue-based testing as the criterion standard, the specificity of ctDNA testing is high, meaning that targetable alterations detected in ctDNA are also typically evident in the tumor itself.[15] The sensitivity is lower, however; approximately 30% of targetable lung cancer alterations identified by tissue-based testing were not identified by ctDNA tests.[16] Thus, patients with negative ctDNA test results are recommended to undergo tissue-based testing to rule out a false-negative result.[16] The role of ctDNA in other cancers is less established, but in general, the same principle holds: Its specificity is higher than its sensitivity.[17]

However, most patients with cancer do not have a targetable alteration. Less than 15% of US patients with cancer were eligible for targeted therapy in 2020.[18] This has increased from 5% in 2006, but still leaves most patients with cancer without a targeted therapy option. Thus, the major limitation of ctDNA in therapy selection is less about variant detection and more about drug discovery. Even in the original indication of non–small cell lung cancer, less than one-third of patients have targetable alterations. Furthermore, identifying a targetable alteration does not imply efficacious treatment for lung cancer exists, as targeted therapies show at best modest benefit, with many not even tested for their effect on overall survival (eTable in the Supplement).

While more targetable alterations will undoubtedly be found with time, many are likely to be rare, making it increasingly difficult to demonstrate whether efficacious treatment exists. This reflects the "long-tail problem": For any given cancer, there are only a few cancer genes mutated at relatively high frequencies, yet many others mutated at low frequencies.[19] For example, among the 8 targeted lung cancer alterations listed in the National Comprehensive Cancer Network guidelines, 4 are present in less than 5% of patients. Not surprisingly, given the difficulty in recruiting study patients, the data on the efficacy of treatment are weak and are based on single-group studies (eTable in the Supplement). This leads to a particular irony of precision oncology: As our drugs become more precise, small samples make the evidence for their efficacy less precise.

Central Clinical Question: How Many Genetic Alterations Should Be Tested For?

Not only does testing for more alterations incorporate more alterations of questionable clinical utility, it also makes testing more costly.[20] More alterations also make it more difficult to assess analytic validity. Ideally, each alteration would be validated against a known reference standard. However, with many alterations, that becomes particularly onerous. Analytic validity is not a hypothetical problem: An investigation of patients with metastatic prostate cancer found low congruence among 2 of these multiple-gene panels.[21] In over half of the 40 patients, the 2 tests yielded different answers about which alterations were present.

Response to Therapy

Background and Theoretical Case

Evaluating response to therapy is an important aspect of cancer care. In hematologic malignant neoplasms, testing for minimal residual disease (MRD)—measurable evidence of persistent cancer following therapy—has been a long-standing practice.[22] While the presence of MRD is associated with worse patient outcomes, the clinical utility of MRD testing in informing therapeutic decisions is subject to debate.[23] In solid tumors, response to therapy has been typically assessed using imaging.[24] Circulating tumor DNA tests have been proposed as an MRD testing equivalent for solid tumors, as ctDNA is theoretically more sensitive for residual cancer.

Evidence Base

Levels of ctDNA correlate with changes in tumor burden over time in an individual, such as following surgery or chemotherapy.[25] Studies have shown prognostic association between patients with ctDNA-positive findings and poor clinical outcomes in colorectal cancer,[26,27] breast cancer,[28] lung cancer,[7,29] and urothelial carcinoma.[30]

There is a strong interest in reducing adjuvant chemotherapy.[31] Tests for ctDNA have been proposed as a means to guide adjuvant therapy following surgery, particularly in stage II colon cancer, where the conventional high-risk clinical features are not reliably associated with who will benefit.[32] The DYNAMIC study[33] randomized patients to standard care or ctDNA management (patients with ctDNA-positive results received adjuvant therapy, those with ctDNA-negative results did not); the intervention reduced adjuvant therapy by half (15% vs 28%) with no effect on recurrence or death.

Central Clinical Question: Can ctDNA Reduce the Use of Adjuvant Chemotherapy Without Negatively Affecting Survival?

Reducing adjuvant therapy in resected tumors is a worthy goal for ctDNA testing. The DYNAMIC study[33] is an exemplar in terms of testing the test-treatment combination vs no testing at all. In other trials, all participants receive ctDNA test results and the randomization involves various adjuvant treatment strategies.[34] The DYNAMIC study design reframes the question to ask whether the test itself adds value, rather than what to do about a test result (implicitly assuming all should be tested).

Nevertheless, de-escalating adjuvant therapy remains challenging. There are reasonable concerns that ctDNA will only increase adjuvant therapy because, in practice, it will be used in addition to current high-risk criteria, not as a substitute.[35]

Disease Surveillance Following Cancer Treatment

Background and Theoretical Case

Another potential use of ctDNA tests is disease surveillance in patients with cancer. In this context, surveillance refers to regular follow-up testing of asymptomatic, previously treated patients with cancer. The goal is to find early signs that a cancer has returned, in essence, screening patients with a history of cancer for cancer recurrence. The detection of the reemergence of ctDNA from the original tumor is likely to constitute a highly specific finding: powerful evidence that the cancer has come back.

However, earlier detection of cancer recurrence, in and of itself, does not mean that patients are being helped. For patients to live longer (or live better), treatment initiated earlier must confer some benefit over treatment initiated later.

Evidence Base

There is no such evidence for ctDNA-based surveillance. A systemic review of 11 randomized clinical trials of imaging-based surveillance in patients with cancer[36] found no reduction in mortality, despite earlier detection of recurrence (eFigure in the Supplement). This suggests that treatment of asymptomatic cancer recurrence offers no advantage over treatment initiated after symptoms occur.

Although this could be interpreted as a null finding, we would argue that it is, in fact, evidence of harm. First, there is the general anxiety associated with cancer surveillance.[37] More importantly, patients whose cancers do recur now live longer with the knowledge that their cancer has come back. They are subjected to additional therapies and their toxic effects earlier, at a time when they would otherwise be asymptomatic. The breast cancer community shares this assessment of harm in recommending that clinicians should not offer routine laboratory tests or imaging for the detection of breast cancer recurrence in the absence of symptoms.[38]

Central Clinical Question: Is ctDNA Surveillance Any Better Than Imaging-Based Surveillance?

While ctDNA surveillance may be a substantial improvement over imaging surveillance, that remains to be proven. Surveillance with ctDNA could advance the time of diagnosis of recurrence (ie, provide a longer lead time), which could lead to improved therapeutic efficacy. Alternatively, it could lead to more specific detection of resistance alterations that, in turn, result in better therapy selection. However, both are simply hypotheses awaiting confirmation in rigorous randomized clinical trials.

Diagnosis of Suspected Cancer

Background and Theoretical Case

The utility of ctDNA tests to evaluate patients with symptoms suggestive of cancer hinges on their ability to detect cancers at multiple sites and to distinguish among them. Testing symptomatic patients has some theoretical advantages over screening. First, there should be more cancer signal to detect; patients with symptomatic cancers would be expected to shed more ctDNA than those with asymptomatic cancers. Second, the higher cancer prevalence in symptomatic patients should enhance the positive predictive value of the test.

Evidence Base

Higher-stage tumors shed more ctDNA into the blood and are therefore more likely to be detectable with ctDNA testing.[39] A large fraction of cancers identified in demonstration projects of multicancer screening have been late-stage cancers (**Figure**), some of which were concurrently being evaluated because of symptoms (ie, in the process of presenting clinically). Thus, ctDNA testing might play a role in the diagnosis of suspected cancer.

In June 2023, GRAIL (a manufacturer of a ctDNA test that reportedly can detect 50 cancers[40]) reported preliminary results in patients with symptoms concerning for cancer.[41] The single-group study enrolled approximately 6000 patients in England and Wales who were referred by their primary care clinicians for symptoms suggestive of gynecologic, lung, or upper or lower gastrointestinal tract cancers or nonspecific symptoms that could indicate cancer (eg, unexplained weight loss, abdominal pain, and the recent onset of fatigue). Patients were followed up for 12 months to correlate ctDNA test results with the final diagnoses obtained by conventional evaluation.[41] Sensitivity of ctDNA was low (66%), meaning 34% of all cancers diagnosed were missed by the test (124 of 368). Sensitivity for stage I cancer was very low (24%), consistent with other studies. An additional 79 patients had a positive cancer signal but were not diagnosed with cancer during the study period. Given the short follow-up of this study, it is uncertain whether these patients had false-positive findings or have yet to be diagnosed with cancer.

Central Clinical Questions: At What Point Would a ctDNA Test Be Introduced Into the Conventional Workup, and How Would It Help?

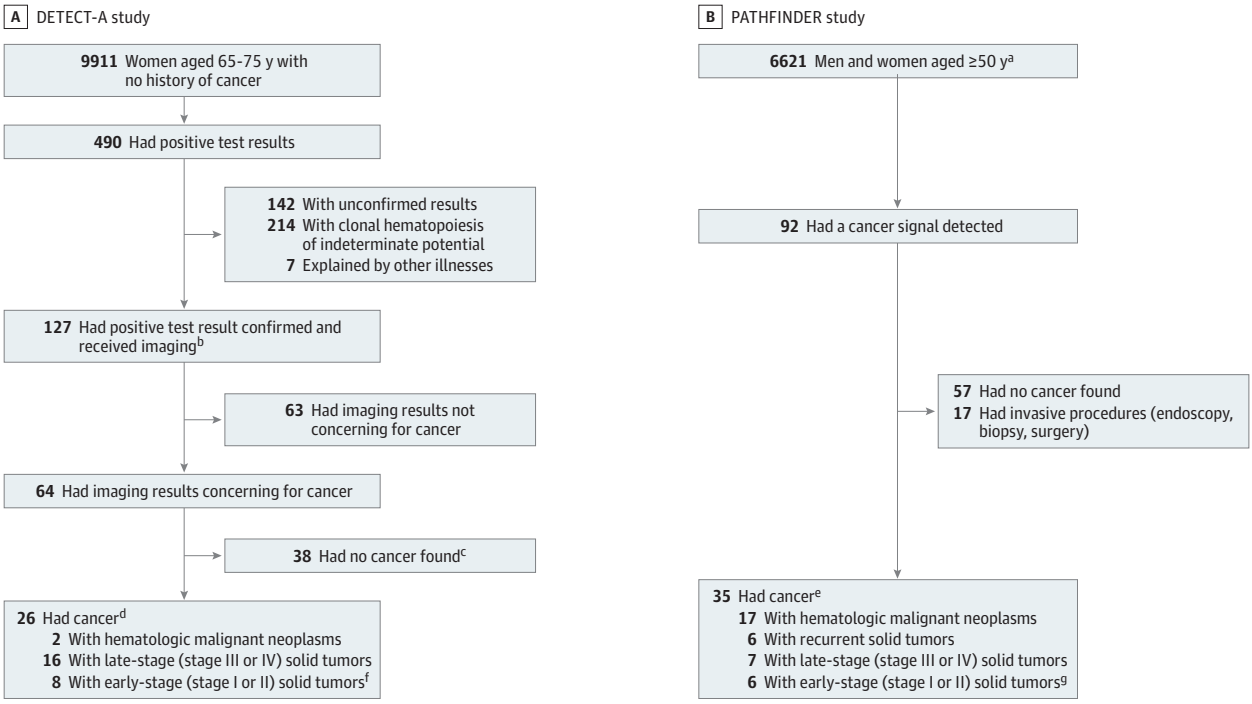
The challenge is to think critically about how ctDNA testing could add to the current diagnostic evaluation of patients suspected of having cancer (eg, with imaging, colonoscopy), as it will almost certainly add cost. A ctDNA test could be the initial diagnostic test. However, based on the aforementioned preliminary data, a negative test result cannot be used to rule out disease. A positive ctDNA result combined with the likely tumor of origin might help direct subsequent evaluation, but the question is whether the information is any better than that contained in the presenting symptoms. Alternatively, ctDNA testing might be reserved for the subset of patients with nonspecific symptoms or those in whom the conventional diagnostic evaluation is unrevealing. The diagnostic yield in this subset is likely to be low, however, and positive results are more likely to be a false positive. Regardless of where in the diagnostic pathway ctDNA tests are introduced, their utility needs to be demonstrated in a randomized trial.

General Population Screening

Background and Theoretical Case

Some investigators are proposing ctDNA tests be used for cancer screening, often labeled as multicancer early detection (MCED) tests for this indication.[42] The notion is appealing: a single blood test that

Figure. Population Flow Diagram and Yield of Screening Using Multicancer Detection Tests in 2 Demonstration Projects: DETECT-A[43] and PATHFINDER[44,45]



[a] Of these, 3681 (56%) had a history of cancer, smoking, or hereditary risk.

[b] Of these, 116 underwent positron emission tomography–computed tomography.

[c] Of these, 22 individuals underwent 30 invasive procedures (including 3 surgical operations).

[d] Of these, 11 were found after physician-initiated imaging based on symptoms.

[e] Of these, diagnostic testing was initiated in 2 individuals before multicancer detection test results were confirmed; 1 individual had 2 cancers diagnosed.

[f] Includes lung (n = 3), thyroid, uterine (n = 2), ovary, and colon.

[g] Includes oropharyngeal, liver, pancreas, small intestine, uterine, and bone.

could detect many types of cancer, particularly as most cancers currently do not have an established screening test. Furthermore, a single test could simplify and standardize cancer screening, which is currently a complex process involving multiple individual tests, many of which are observer dependent (eg, mammography, colonoscopy). Most proponents, however, are suggesting multicancer tests as a complement to existing screening tests, not as a substitute.

Evidence Base

The Figure provides a schematic overview of 2 demonstration projects that have documented the findings of multicancer detection testing in prospective cohorts,[43-45] highlighting 3 challenges to MCED screening. First, because the tissue being sampled is blood, hematologic cancer signals are disproportionately detected. Developers have had to work hard to more stringently exclude cancerlike hematologic signals.[43,46]

Second, the most commonly detected solid tumors are late-stage or recurrent cancers. While this is not surprising, given that these cancers are more likely to shed ctDNA, the utility of screening for advanced cancers is questionable, particularly since many were in the process of being detected because of symptoms. Third, most patients with a positive test result do not have a cancer identified. This is typical of screening: The low prevalence of cancer means positive tests are less likely to represent clinically relevant disease and more likely to represent false-positive results or overdiagnosis.

It is important to note that less than one-third of all cancers diagnosed during the 2 demonstration projects were detected by the multicancer screening test (26 of 96 [27%] in DETECT-A [Detecting Cancers Earlier Through Elective Mutation-Based Blood Collection and Testing][43] and 35 of 121 [29%] in PATHFINDER[44,45]). The remainder were either detected by conventional screening (25% and 40%, respectively) or presented clinically despite screening (48% and 31%, respectively). This is a well-known phenomenon of cancer screening: Screening tends to miss the fastest growing, most aggressive cancers. This limits the potential benefit of screening and makes its harms yet more relevant.

False-positive results—or false alarms—are a common adverse effect of screening tests. They trigger fear and more testing.[47,48] However, in multicancer testing, they produce a unique challenge: How do we know it is truly a false alarm? One proposed subsequent test for an MCED cancer signal is whole-body positron emission tomography–computed tomography (PET-CT). However, if the PET-CT finds no abnormality, physicians are left with a conundrum: Does the patient truly not have cancer, or do they have a cancer that cannot be found with current technology? This question will only be resolved with long-term follow-up of patients with apparently false-positive results.

Table 1. Active Multicancer Detection Studies Accepting Healthy Volunteers in ClinicalTrials.gov[a]

Test	Trial name	Study type	Sample size	Study population	Primary outcome[b]	End date
Multiple assays	Collecting Blood Samples From Patients With and Without Cancer to Evaluate Tests for Early Cancer Detection	Observational	2000	Aged 40-75 y, with cancer or high suspicion of cancer or healthy participants	Test performance	February 2025
OverC (ctDNA; Guangzhou Burning Rock Dx Co, Ltd)	A Prospective Multi-Cancer Early-Detection Test in Asymptomatic Individuals (PREVENT)	Observational	12 500	Aged ≥40 y	Test performance	December 2028
OverC (ctDNA; Guangzhou Burning Rock Dx Co, Ltd)	Pan-Cancer Early Detection Project (PREDICT)	Observational	14 026	Aged 40-75 y, with cancer or with benign diseases in tumor sites or healthy participants	Test performance	March 2023
ctDNA (Wuhan Ammunition Life-tech Co, Ltd)	Clinical Study of Pan-cancer DNA Methylation Test in Plasma	Observational	3000	Aged ≥18 y, with high suspicion of cancer or noncancerous diseases or healthy participants	Test performance	August 2023
Elypta (metabolomic)	Multi-Cancer Early Detection (MCED) of Firefighters	Observational	2000	Actively working firefighters	Test performance	December 2030
Elypta (metabolomic)	GAGomes for Multi-Cancer Early Detection in High-Risk Adults	Observational	1256	Aged 55-80 y with significant smoking history	Test performance	March 2025
Elypta (metabolomic)	GAGomes for Multi-Cancer Early Detection in Asymptomatic Adults	Observational	9170	Aged 18-80 y, with cancer or healthy participants	Test performance	March 2025
Harbinger Health (ctDNA)	Development and Validation of Harbinger Health Test for Early Cancer Detection	Observational	10 000	Aged 20-79 y, with cancer or healthy participants	Test performance	July 2025
Adela Inc (ctDNA)	cfDNA Assay Prospective Observational Validation for Early Cancer Detection and Minimal Residual Disease	Observational	7000	Aged ≥40 y, with cancer or healthy participants	Test performance	December 2026
Freenome (multiomics)	The Sanderson Study: A Case Control Study for the Development of Multiomics Blood Tests for Cancer Screening	Observational	8000	Aged ≥30 y, with cancer or healthy participants	Test performance	September 2025
Freenome (multiomics)	The Vallania Study: A Case Control Study for the Development of Multiomics Blood Tests for Cancer Screening	Observational	5400	Aged ≥30 y, with cancer or healthy participants	Test performance	December 2024
Galleri (ctDNA; GRAIL)	PATHFINDER 2: A Multi-Cancer Early Detection Study	Observational	20 000	Aged ≥50 y, healthy participants	Test performance[c]	July 2026
Galleri (ctDNA; GRAIL)	REFLECTION: Real World Evidence for Learnings in Early Cancer Detection, a Clnical Practice Learning Program for Galleri	Observational	35 000	Aged ≥22 y, healthy participants	Test performance	August 2026
Galleri (ctDNA; GRAIL)	The SUMMIT Study: Cancer Screening Study With or Without Low Dose Lung CT to Validate a Multi-Cancer Early Detection Test	Observational	13 035	Aged 55-77 y, high-risk smokers	Test performance	August 2030
Galleri (ctDNA; GRAIL)	Does Screening With the Galleri Test in the NHS Reduce the Likelihood of a Late-Stage Cancer Diagnosis?	Randomized clinical trial	140 000	Aged 50-77 y, healthy participants, intervention blood test with results vs control standard care (blood collection only)	Numbers of stage III and IV cancers diagnosed	February 2026

Abbreviation: ctDNA, circulating tumor DNA.

[a] Search criteria consists of "multi-cancer" with the filters: accepts healthy volunteers and not yet completed.

[b] Test performance includes evaluation of diagnostic yield, sensitivity, specificity, positive and negative predictive value, and tissue of origin.

[c] Also measuring the number of invasive procedures among false-positive results.

Overdiagnosis refers to the detection of abnormalities that meet the pathological criteria for cancer but will not cause either symptoms or death.[49] While much less common than false alarms, overdiagnosis is the most consequential harm of screening, as it triggers unneeded treatment. However, MCED tests themselves will likely cause little overdiagnosis (with the exception of hematologic malignant neoplasms) simply because small, innocuous, nonprogressive cancers are not expected to shed ctDNA.[46,50] Nevertheless, subsequent imaging triggered by MCED tests (eg, PET-CT) will result in overdiagnosis (eg, the incidental detection of tumors in the thyroid, kidney, adrenal glands). While more targeted evaluation (eg, colonoscopy) could reduce this risk, the appropriate diagnostic algorithm to evaluate a cancer signal is unknown.

Ironically, that MCED tests themselves pose a low risk of overdiagnosis highlights their potential weakness in screening: a low sensitivity for early-stage cancer (approximately 40% across different cancers and tests).[51-53] For screening to lower cancer mortality, it must advance the time of diagnosis of tumors destined to cause death. Thus, a conundrum exists: While low early-stage sensitivity may be a good thing—particularly in those cancers where screening or incidental detection is known to cause overdiagnosis (eg, breast, lung, kidney, prostate, thyroid, and melanoma)—it may also limit the ability of MCED tests

Table 2. Harms of Screening

Harm	Description	No. of individuals affected	Effect on individual
Overdiagnosis	Patients are diagnosed and treated for a cancer not destined to progress to cause symptoms or death. Some experience complications of treatment.	Few	Large
Earlier detection of aggressive cancer and/or no change in death	Patients live longer with the knowledge they have a deadly cancer and experience interventions and their toxic effects at a time they would otherwise be asymptomatic.	Few	Large
Financial toxicity of subsequent evaluation	While screening itself typically has few out-of-pocket costs, it can trigger subsequent diagnostic evaluations with substantial out-of-pocket costs.	Several	Moderate
False alarm	People with abnormal screening test results generally do not have cancer, but before they are pronounced "cancer free," many have to go through multiple tests. Throughout the process, many will worry about whether they have cancer. Some will never be reassured that they are, in fact, healthy.	Many	Small

to detect aggressive cancers early. On the other hand, it is possible that MCED tests are able to separate the wheat from the chaff, that is, to discriminate between the 2 subsets and detect only those cancers destined to cause problems. To determine which hypothesis is correct will require a randomized clinical trial.[54]

Unfortunately, most ongoing trials of multicancer testing in healthy volunteers have no control group (**Table 1**). The lone exception is a randomized trial of Galleri in England, a partnership between the National Health Service and Galleri's manufacturer, GRAIL.[55] The trial has recruited 140 000 healthy individuals who have been randomized (1:1) to either the intervention (3 annual screens with Galleri) or usual care.[56] The study is expected to be completed in February 2026 and uses the number of stage III and IV cancers as the primary outcome.[57]

While the size and scope of this trial are commendable, its primary outcome is problematic. A reduction in late-stage cancer would be evidence that screening is advancing the time of diagnosis for cancers otherwise destined to present at a late stage. However, that does not constitute evidence that patients are being helped. Mortality could be unchanged, and patients may only live longer with the knowledge they have a deadly cancer (while experiencing interventions and their toxic effects at a time they would otherwise be asymptomatic). A more appropriate outcome would be all-cancer mortality, given that the test can detect 50 cancers. Furthermore, because cancer deaths are a substantial component of all deaths, it has been argued that this trial is sufficiently large (particularly with longer follow-up) to test all-cause mortality.[58] This would provide irrefutable evidence of patients being helped.

Central Clinical Question: Does ctDNA Screening Really Help People Live Longer or Live Better?

Little is known about the population effects of ctDNA and/or multicancer detection screening, other than it will certainly be expensive. Galleri is currently priced at $949 a test and is recommended annually for individuals 50 years and older.[59] With approximately 100 million US residents in this age group, that is about $100 billion a year, or about 10 times the 2023 budget for the Centers for Disease Control and Prevention.[60] Were the Medicare Multi-Cancer Early Detection Screening Coverage Act to become law, Medicare would be mandated to pay about half that cost. Clearly, this cost warrants a rigorous demonstration of benefit—that patients are living longer or living better—in a randomized clinical trial.

In recognition of this, the National Cancer Institute (NCI) has initiated a 3-step process to investigate multicancer screening[61] and will first validate the performance of various MCED tests in an independent reference set of 1000 patients known to have cancer and 1000 controls. The second step will select 2 tests for further investigation in a trial randomizing 24 000 people into 3 groups (2 intervention groups and 1 control group). This study will evaluate the feasibility of protocol-defined algorithms for diagnostic testing following abnormal screening test results in preparation for a larger trial. Finally, the larger trial will consist of up to 3 test groups and a control group receiving standard of care screening alone. It is planned to test all-cancer mortality, over a period of 7 to 8 years, and include up to 300 000 participants, making it the largest cancer screening trial ever performed.[62]

The conundrum of cancer screening is that only a few participants can potentially benefit, while all can be potentially harmed. While the potential benefit of screening (avoiding a cancer death) is more important than any one of its harms (**Table 2**), many more people experience the harms than the benefits. Thus, the critical question is whether the benefits for the few are sufficiently large to warrant the associated harms for the many. To address this question, randomized clinical trials of MCED testing must not only measure the effect screening on death, but also provide a full accounting of its harms.

Limitations

This review has some limitations. It is exploratory in that it attempts to assess the available evidence and organize it into clinically relevant indications. However, ctDNA testing is an emerging and rapidly evolving field; thus, the terminology is inconsistent, and relevant studies may have been missed. Our review is also limited because there is little evidence addressing the clinical utility of ctDNA and because what exists is weak (eg, observational studies without patient-centered outcomes).

Conclusions

Circulating tumor DNA tests are being promoted for therapy selection, response to therapy, disease surveillance, diagnosis of sus-

pected tumor, and screening for cancer. Numerous studies are ongoing, but randomized clinical trials assessing their effect on patient-centered outcomes are rare. The potential of these tests to improve care in selected indications must be proven, as they will add cost, complexity, and unintended adverse effects for patients.

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